REMARKS

Claims 56-69 were previously pending. Claims 58, 59, 64 and 69 have been canceled and claims 70-78 have been added. Accordingly, claims 56, 57, 60-63, 65-68 and 70-78 are presented for examination. Reconsideration is requested.

No new matter has been added by virtue of the instant amendments and newly added claims. Specifically, the amendment of claim 56 is supported by the specification, for example at page 16, lines 7-9 and original claims 1 and 11, which describe treatment of an obstructed biological conduit such as an artery or vein. The amendment of claim 57 is supported by the specification, for example at page 12, line 11. The amendment of claim 62 is supported by specification, for example by original claim 10. The amendment of claim 63 is supported by the specification, for example at page 17, lines 2-4. New claims 70-77 are supported by the specification, for example at page 16, line 27 to page 17, line 11. New claim 78 is supported by the specification, for example at page 12, line 11.

I. OBJECTIONS TO THE SPECIFICATION

The Examiner has identified minor errors in the specification and has invited their correction. Applicant sincerely thanks the Examiner for his careful attention to the specification, and has amended the specification to correct the errors identified by the Examiner, as well as other typographical errors of which Applicant is now aware upon further review.[1]

II. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 56-69 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement on the grounds that the specification does not provide working examples demonstrating treatment of obstructed arteries or veins in a human patient or experimental model via *in vivo* administration of an elastase preparation. *See* Office Action, Sections 12-14.

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1 With regard to page 9, lines 5-8, Applicant respectfully points out that "benign biliary stricture" is one subtype of biliary stricture.

Applicant respectfully points out that the specification teaches all that is necessary to enable one of ordinary skill in the art to practice the invention as claimed, without undue experimentation, and in this regard submits herewith the Declaration Under 37 C.F.R. § 1.132 of F. Nicholas Franano, MD (the "Franano Declaration"). As taught by the specification, a dose titration was performed to determine optimal dosage for administration according to the methods of the invention. *See* Specification at p. 15; Franano Decl. ¶ 6 & Table 1. The methods of the invention were applied to produce dilation of arteries and veins in rabbits and pigs, two art-recognized models of the human cardiovascular system. Franano Decl. ¶ 4. Upon local administration to the wall of arteries or veins, both porcine and recombinant human elastase resulted in proteolysis of elastin in the vessel wall and led to enlargement of the diameter of the treated vessel, as well as enlargement of the lumen of the treated vessel. *Id* ¶¶ 7-18. Thus, the data and opinions set forth in the Franano Declaration provide persuasive evidence that the specification enables one of ordinary skill in the art to practice the presently claimed invention. *See id* at ¶¶ 3, 19.

III. REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 56-69 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to mention a particular condition in/of the artery or vein being treated; and claim 66 was rejected under § 112, second paragraph, as indefinite for recitation of the phrase "susceptible to." *See* Office Action at pp. 5-6, Section 15.

In accordance with the Examiner's suggestion, claim 56 has been amended to recite that the artery or vein being treated is "obstructed." Claim 66, as amended, no longer recites the phrase "susceptible to obstruction."

Accordingly, the rejections under § 112, second paragraph have been obviated by the instant amendments and should be withdrawn.

IV. REJECTIONS UNDER 35 U.S.C. § 102

A. Rejection Over Wolinsky

Claims 56, 59-63 and 67-68 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,636,195 ("Wolinsky"). For the following reasons, Wolinsky does not anticipate the claims as presently amended.

Wolinsky concerns the solubilization of obstructive plaques in the lumen of arteries by administering a solubilizing liquid, optionally including a collagenase, in order to disrupt the plaque. (Wolinsky, col. 4, lines 40-58). As Wolinsky explains:

> The collagenase cleaves the collagen which is the main supportive structure of the plaque. The plaque body then collapses. This result together with the solubilization of the fat and other components of the plaque serves to decrease markedly the total volume of the plaque and increase the flow of blood in the artery.

Id, col. 4, lines 45-51.

The claims have been amended to require administering a composition comprising an elastase, thereby obviating this rejection. Wolinsky teaches administering a composition comprising a collagenase, but neither teaches nor suggest administering a composition comprising an elastase.[2] Moreover, Wolinsky teaches removing an arterial plaque or reducing its volume, but fails to teach or suggest increasing the diameter of an artery or vein, as required by the present claims. Nor does Wolinsky teach or suggest causing proteolysis of elastin in the wall of an artery or vein, as required by the present claims.

For each of the above reasons, Wolinsky does not anticipate the presently claimed invention, and the rejection under § 102(b) over Wolinsky should be withdrawn.

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2 The Examiner recognized and acknowledged that Wolinsky "does not teach administering a composition comprising elastase," (*see* Office Action at p. 8, Section 19), and did not apply Wolinsky as an anticipatory reference against claims 57 and 58, which recited administering a composition comprising an elastase.

B. **Rejection Over Dev '710**

Claims 56-63, 65 and 67-68 were rejected under 35 U.S.C. § 102(a) as anticipated by U.S. Patent No. 5,944,710 to Dev *et al.* ("Dev '710"). Dev '710 teaches the use of electroporation in order to enhance delivery of a therapeutic agent directly into the cells of a blood vessel wall. (Column 3, lines 25-40). Dev '710 teaches that its electroporation method is applicable to "any composition which would have a desired biological effect at the site of electroporation," (col. 4, lines 62-63), including elastase (col. 5, line 9) and nucleic acids. (Col. 5, lines 18-20).

Dev '710 does not teach or suggest enlarging the diameter of an artery or vein, and fails to teach or suggest administering elastase in a dose sufficient to cause such enlargement. However, the Examiner posited that "administration of some quantity of said composition comprising collagenase/elastase according to Dev et al's method would upon its administration, inherently function in the same way (i.e. proteolysis of elastin in the wall of artery or vein) as instantly claimed." *See* Office Action at p. 7, Section 18 (emphasis added). Applicant respectfully points out that proteolysis of elastin in the wall of an artery or vein can be achieved without causing dilation of the treated vessel, as required by the pending claims. As shown below, the prior art taught the use of low doses of elastase to obtain limited digestion of elastin in a vessel wall in order to achieve other therapeutic benefits while avoiding dilation of the vessel, which the prior art regarded as unsafe and undesirable in a therapeutic setting.

In this regard, Applicant invites the Examiner's attention to Maillard *et al.*, *Gene Therapy* 5: 1023-1030 (1998) ("Maillard"), which was previously considered in connection with this application.[3] Maillard teaches treating an artery with a low dose of elastase to improve the penetration of nucleic acid vectors used for gene therapy, while avoiding dilation of the artery. As Maillard explains:

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3 Maillard was submitted and made of record as Reference AA in the Supplemental Information Disclosure Statement filed on July 3, 2003 (paper no. 16).

> Since elastin is a major component of the IEL [Internal Elastic Lamina], pre-incubation with elastase may permeate the IEL to adenoviral recombinant vectors and therefore enhance the efficiency of medial transduction, a critical step for many arterial gene strategies.

Maillard at 1023, right column, first full paragraph.

In view of the perceived danger that elastase treatment might cause arterial dilation and aneurysm formation:

> a dose ranging pilot study (group 1) was performed to determine the highest concentration of elastase that produced neither angiographically detectable aneurysms nor increases in the lumen diameter, or light microscopically detectable damage to the IEL or the media. The initial dose of 2.625 IU was chosen after literature review and doses were decreased logarithmically until the safest dose was identified.

Id. at 1028, right column, 2nd full paragraph. By performing a dose ranging study in rabbits, the authors identified 2 x 10^{-7} IU elastase as a dose that could safely be used without altering the diameter of the artery:

> The highest elastase dose used in this experiment (2.625 IU) led to macroscopically and angiographically visible aneurysmal dilatation of the iliac artery. . . . Lower doses (2 x 10^{-2} IU and 2 x 10^{-3} IU) also induced aneurysm formation. Aneurysm formation was not observed after incubation with 2 x 10^{-4} IU, however light microscopic examination disclosed IEL disruption and necrosis of the superficial layers of the media. The IEL was microscopically preserved at 2 x 10^{-5} IU, but necrosis of the two or three innermost SMC layers of the media was frequently observed. Small areas of SMC necrosis, limited to the superficial layer, were observed at 2 x 10^{-6} IU. However, **at 2 x 10^{-7} IU, elastase did not evoke vascular injury**, as assessed by angiographic, macroscopic, light microscopic and ultrastructural examination.
>
> * * *
>
> Both at 3 days and 7 weeks following pretreatment with elastase (2 x 10^{-7} IU) or saline, **no vessel dilatation or aneurysms were observed** and lumen diameters did not significantly differ between groups . . . .

Id. at 1024, left column, first full paragraph; right column (emphasis added).

In other words, the prior art regarded arterial dilation as a form of "vascular injury" to be avoided by choosing an appropriately low dose of elastase. *See id.*, Abstract. ("After an initial safety dose ranging study, rabbits underwent balloon abrasion of the iliac endothelium followed by local incubation of either elastase (2×10^{-7} IU over 5 min) or saline using a double balloon catheter (DBC)."). At this dose, elastin was effective at improving penetration of the gene transfer vector, without causing arterial dilation:

> The elastic tissue forms a network of fibers and lamellae within the vascular wall, characterized by a three-dimensional architecture. The internal elastic lamina adjacent to the epithelium has a scalloped appearance with small gaps or fenestrae scattered throughout this sheet. Most of the openings of the fenestrae are bridged by fine elastic fibers that give the fenestrae a sieve-like appearance. Despite improvement in transfection efficiency after elastase incubation, neither light nor electron microscopic abnormality of the principal sheet of the internal elastic lamina were seen. **This suggests that elastase, at the concentrations used, may degrade the fine elastic fibers occluding the gaps rather than the condensed elastic fibers constituting the principal sheet itself.** This may in turn open breaches or holes between the elastic mesh without actual degradation of the condensed sheet, resulting in improved penetration of adenoviral vectors into the media. This hypothesis is supported by the fact that **both at 3 days and 7 weeks post-procedure, no vessel dilatation or aneurysms were observed and there was no increase in lumen diameters.**

Id. at 1026, right column (emphasis added).

The experimental results reported in Maillard show that beneficial therapeutic effects sought by the prior art from elastase (*e.g.*, penetration enhancement) can be achieved without causing dilation of the vessel. Thus, it cannot be said that dilation of a blood vessel, as presently claimed, is inherently achieved by the therapeutic administration of elastase. Maillard, which was published in 1998, also demonstrates the conventional wisdom, prior to the present invention, that arterial dilation is a form of "vascular injury" that should be avoided by choosing an appropriately low dose of elastase for therapeutic purposes. In other words, the prior art

taught away from the use of elastase to obtain therapeutic dilation of an artery or vein, as presently claimed.

Nothing in Dev '710 contradicts or refutes this accepted view, or suggests the use of elastase in such a way as to cause vascular dilation. Indeed, since both Maillard and Dev '710 are both concerned with enhancing penetration of therapeutic agents into the vascular wall, the suggestion in Dev'710 to combine electroporation with elastase treatment would have conveyed to one of ordinary skill in the art the use of elastase at a safe low dose, as taught by Maillard, in order to enhance penetration while avoiding proteolysis of elastin to a degree that will cause vascular dilation, which the art viewed as a form of vascular injury.

It was only the present inventor who rejected the art-accepted view and, to the contrary, taught the therapeutic administration of elastase so as to achieve proteolysis of elastin to a degree that causes dilation of an artery or a vein in a human subject. Such use of elastase is neither taught nor suggested in Dev '710.

A subsequent patent issued to the same inventors who are named in Dev '710 provides further evidence that the present invention represents a radical departure from prior art thinking. Submitted herewith is U.S. Patent No. 6,347,247 B1, issued to Dev *et al.* in 2002 on an application filed on May 7, 1999 ("Dev '247"). Dev '247 teaches applying electric impulses to a vessel in order to induce vasodilation. Dev. 247 describes a completely different mechanism of vasodilation than is required by the presently pending claims:

> [T]he induction or increase of vessel vasodilation by an electric impulse appears to result either from a direct effect caused by the electric current applied to the vessel, or an indirect effect resulting from the release or stimulation of factors that promote vasodilation, such as the release of endothelium derived relaxation factors (EDRF) currently identified as nitric oxide (NO) or other vasodilating substances triggered by the electrical pulses applied to the cells of the vessel.

Dev '247 col. 5, lines 16-24.

Dev '247 teaches that electrically induced vasodilation can be combined with concurrent administration of compositions that inhibit cell proliferation, such as elastase. *Id.* at col. 15, lines 27-30, 35. Even though the inventors of Dev '247 were concerned with achieving vascular dilation, they still did not teach or suggest the use of elastase for this purpose, but only for inhibiting cell proliferation. In other words, the teachings of Dev '247 are consistent with the well established, art-accepted view, reflected in Maillard, that it would be dangerous and unsafe to administer elastase so as to degrade elastin to such a degree as to cause dilation of the vessel.

Thus, the present invention reflects a radical departure from prior art thinking, and for the first time teaches the administration of a composition comprising elastase so as to achieve proteolysis of elastin that leads to enlargement of the diameter of an artery or vein in a human subject. Such use of elastase compositions is neither taught nor suggested in Dev '710.

For each of the above reasons, the rejection under § 102(a) over Dev '710 should be withdrawn.

V. REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 56-69 were rejected under 35 U.S.C. § 103(a) as obvious over Wolinsky in view of Dev '710.

The deficiencies of Wolinsky are discussed above, including the fact that Wolinsky does not teach or suggest administering a composition comprising an elastase, and further fails to teach or suggest treating an artery or vein so as to increase its diameter.

The deficiencies of Dev '710 are also discussed above, including the fact that Dev '710 fails to teach or suggest administering a composition comprising elastase so as to obtain proteolysis of elastin that leads to dilation of an artery or a vein in a human subject.

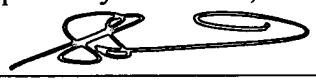
Accordingly, the combination of Wolinsky and Dev '710 does not provide the invention as presently claimed, and Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In light of the above remarks, Applicant respectfully requests that the Examiner enter this Amendment and allow the claims as herein amended. The Examiner is invited to call the undersigned attorney (212) 859-8973 if a telephone call could help resolve any remaining issues.

Date: May 17, 2005

Respectfully submitted,



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